Muscle and Tendon related Adverse Event Prevalence and Incidence Rates with Statin Use

Technical Report

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Sanjay Mehrotra[1]

Kibaek Kim[1]

David M Liebovitz[2]

[1]Industrial Engineering and Management Sciences, Northwestern University, Evanston, Illinois

[2]Department of Medicine, Division of General Internal Medicine; Department of Preventive Medicine, Division of Health and Biomedical Informatics; Feinberg School of Medicine of Northwestern University, Chicago, Illinois

Abstract

Background

A new drug safety communication regarding contraindications and dose limitations for simvastatin was recently issued by FDA to reduce the risk of muscle injury.

Purpose

To study statin associated adverse events (AEs) for patients over time in a large retrospective cohort.

Methods

The authors conducted a case-control study of 15,890 patients prescribed statins at Northwestern healthcare affiliates in Chicago, Illinois, from year 2004 to 2010, matching gender and age. Patient medical records were retrospectively obtained from the Northwestern Medical Enterprise Data Warehouse, excluding patients with age < 30, pregnancy, or cancer diagnosis. AEs and patients taking higher statin doses were identified by ICD-9 codes and creatine kinase (CK) level. The AE prevalence was studied for patients on different statins and compared those with simvastatin in the cohort.

Results

The overall AE prevalence was 5.4%, compared to 0.17% for the controls. Statins were ranked in the following increasing order of AE prevalence: simvastatin (4.48%), atorvastatin (4.78%), pravastatin (6.35%), lovastatin (7.32%), rosuvastatin (7.35%), and fluvastatin (8.29%). The AE prevalence at the highest statin dose was not significantly higher than the overall prevalence for that statin. Approximately 97% of patients reporting AEs did not demonstrate corresponding CK elevations. The AE prevalence was higher in the older and female population.

Conclusion

Since in the current study simvastatin had the lowest AE prevalence compared to the other statins, and the overall prevalence was similar to AE prevalence at the highest dose for all statins, healthcare professionals should carefully monitor patients taking any statin for muscle and tendon related AEs.

Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) are widely used agents for lipid management among patients at risk for cardiovascular disease. Lowering cholesterol levels reduces the risk of coronary heart disease (CHD), and clinical trials have demonstrated that treatment with statins significantly reduces mortality risk from cardiovascular causes with few adverse events (AEs) of myopathy [1-7].

However, studies have also raised concern that the prevalence of statin-related myotoxic effects might be underestimated [8-11]. Risk factors for statin-related myopathy have also been described [8, 9, 12-15]. While many studies have focused on a serious statin AE (e.g., rhabdomyolysis), a recent study queried the FDA Adverse Event Reporting System (FAERS) database to evaluate relative rates of statin related side effects across muscle and tendon categories [16]. FAERS is a self-reporting system that contains information on AE or medication error voluntarily reported by healthcare professionals and patients. The study in [16] presented scores and ranks for muscle and tendon related AEs for six different statins (fluvastatin, rosuvastatin, simvastatin, atorvastatin, pravastatin, and lovastatin) [16]. In addition, by the nature of the reporting data, the AE prevalence and incidence rate could not be studied from FAERS data. The prevalence of statin related AEs is shown to be dose-dependent [8, 12, 17].

The current study used electronic patient data obtained from Northwestern Memorial Hospital (NMH) and Northwestern Medical Faculty Foundation (NMFF) to assess the prevalence and incidence rates for statin related muscle and tendon AEs considered in [16]. The AE prevalence related to higher dose was analyzed for different types of statins. AEs associated with age and gender were also analyzed.

Methods

This study was approved by the Northwestern University International Review Board. The data used in the current study was collected from the Northwestern Medical Enterprise Data Warehouse (EDW). The EDW is a single, integrated database of all clinical and research data for patients receiving care and treatment through Northwestern healthcare affiliates (NMH and NMFF). Diagnosis, medication and laboratory data were assessed for actively managed patients from January 2004 to December 2010. A patient with at least 2 visits during the study period,

and also at least one visit every 18 months was defined as actively managed. Exclusion criteria included patient age < 30 and patients who were pregnant or received a cancer diagnosis (malignant neoplasm, sarcoma, tumors, or carcinoma) during the study period.

Cases and controls were matched by age and gender using the exact number of patients. The ICD9 codes (given in Table 1) were used to identify muscle and tendon related AEs for myalgia and myositis (729.1); myopathy (359.4, 359.8, 359.89, and 359.9); rhabdomyolysis (728.88 and 728.89); joints and tendon (726.5, 726.61, 726.64, 726.71, 726.72, 726.79, and 726.90); muscle injury (728.85); muscle weakness (728.87 and 728.9); and others (710.4, polymyositis; 729.8x, other musculoskeletal symptoms referable to limbs; and 791.3, myoglobinuria). ICD-9 codes related to tendinitis were included based on the PRIMO study [18], in which twenty-five percent of statin-related myopathy patients reported tendon-associated pain. These ICD9 codes ensured inclusion of all muscle and tendon related AEs reported in different studies [16, 18, 19].

Three secondary cases (*ICD9+CK1, ICD9+CK3, and ICD9+CK5 cases*) were studied using the ICD9 codes, and demonstrated elevation of creatine kinase (CK) level greater than 1, 3, and 5 times the upper limit of normal (ULN). These additional subsets were included to increase specificity for non-exertional injury among the ICD9 cases for and included the ICD9+CK5 case as used by Shanahan et al. [9]. The ULNs were defined as 200 IU/L for male and 125 IU/L for female. The elevated CK levels provided an objective criterion, when available, to complement the subjective diagnosis code. Of note, severe myopathy and rhabdomyolysis are defined as CK levels exceeding 10,000 IU/L [20]. *ICD-9 controls* used the ICD-9 codes as described above to identify myopathy patients not taking statins. *ICD9+CK1, ICD9+CK3, and ICD9+CK5 controls* used the ICD-9 and CK levels as described above, again for patients not taking statins. Patient medication data recorded in the EDW was used to identify patients who received a prescription containing the following statins: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. To reduce confounding resulting from interacting medications, patients were excluded if any of the following list of 13 potentially interacting agents was taken during the study period [14]: amiodarone, amlodipine, azole antifungals, colchicine, cyclosporine, dilitiazem, fibrates, interferon, macrolides, nefazodone, oral steroids, protease inhibitors, and verapamil. Patients were excluded from the analyses if they were on a statin with the concomitant medications during the study period.

The AE prevalence was also studied for patients taking the highest dose of statins. Patients were identified taking the highest dose of statins if the highest dose has ever been recorded. The highest doses were 80mg for atorvastatin, pravastatin, simvastatin, and fluvastatin and 40mg for lovastatin and rosuvastatin. The prevalence was calculated as the number of ICD9 cases taking the higher dose of a statin divided by the number of actively managed patients taking a higher dose of the statin.

The age- and gender-adjusted prevalence and incidence rate were calculated for different statin-related AEs. The statin related AE prevalence was calculated as the total number of AEs associated with a particular therapy divided by the total number of patients. The AE incidence rates per person-year were calculated by dividing the total number of AEs with the total number of statin prescription years during the study period. The total statin prescription years was calculated by adding all the days falling between statin start and end date defined in the EDW for each prescription while avoiding double counting for overlapping prescriptions.

Results

A total of 15,890 patients were actively managed on statin therapy during the period. Table 1 summarizes the characteristics of these patients on different types of statins during the study period. Of the actively managed patients on statins 8,724 (54.9%) were male. Atorvastatin and simvastatin were the two most commonly prescribed statins (9,514 and 6,921 patients, respectively). Fluvastatin and lovastatin were the two least prescribed statins (205 and 888 patients, respectively). The mean age of patients on statin therapy was 63.7 years with a standard deviation of 13.6. Column ‘CK checked’ presents the number of patients whose CK levels were checked after taking statins, and also provides the percentage of patients whose CK levels were checked. Column ‘CK checked male’ presents the number of male patients and the percentage with CK checked. CK levels were obtained for only 10.7% (1,704 of 15,890 patients). Patients on fluvastatin had significantly more frequent CK checking than the overall patient population (23.9% vs. 10.7%; p-value < 0.001). There was no statistically significant gender difference among patients for checking CK levels. Table 2 shows the prevalence and the incidence rate for different muscle and tendon related AEs.

Overall Prevalence and Incidence Rate

The overall AE study period prevalence and incidence rates were 5.40% and 2.31 per 100 person-years, respectively. The ratio of AE study period prevalence between women and men was 1.78 (7.10% vs. 4.00%, p-value < 0.001). The statin related relative risk for muscle and tendon related AE reporting was 31.8 (5.40% vs. 0.17%) for ICD9 based AE criteria. Atorvastatin and simvastatin had lower study period prevalence (4.78% and 4.48%, respectively) and incidence rates (2.28% and 2.66 per 100 person-years, respectively) of AEs compared to other statins. AE study period prevalence and incidence rates were significantly higher for patients on rosuvastatin, compared to any statin (7.35% vs. 5.4%; 3.63 vs. 2.31 per 100 person-years). Fluvastatin also demonstrated higher AE study period prevalence and incidence rates (8.29% and 5.09 per 100 person-years), but was not significantly different from the overall rates (5.40% and 2.31 per 100 person-years; p-value = 0.123).

Prevalence Comparison with Highest Dose Statin

Table 3 gives the number of patients taking the highest doses of different statins. Statin doses were not available for all patients. Dose information was available for 28.8% (2737/9514) patients on atorvastatin, 55.3% (870/1574) patients on pravastatin, 42.9% (2967/6921) patients on simvastatin, 80.4% (165/205) patients on fluvastatin, 22.7% (202/888) patients on lovastatin, and 37.5% (710/1891) patients on rosuvastatin. Of actively managed patients taking the highest dose statin, the prevalence of AEs associated with atorvastatin, pravastatin, simvastatin, rosuvastatin, lovastatin, and fluvastatin were respectively 3.9%, 5.6%, 5.6%, 5.7%, 11.4%, and 14.5%. Column ‘P value’ gives the binomial test statistics with the null hypothesis that the AE prevalence at the highest dose statin is higher than the overall prevalence for each statin. The p-values for all statins did not reach statistical significance. The AE prevalence for the highest doses of fluvastatin, lovastatin, and rosuvastatin was marginally higher with p-values of 0.079, 0.109, and 0.074, respectively.

Table 4 gives information on the CK value distribution in the AE population for whom it was checked. For the statin patients reporting AEs based on ICD9 criteria, CK was checked for 259 patients (30%). Only 109 (42%), 27 (10%), and 17 (7%) patients coded for AEs had CK values greater than ULN, 3 times, and 5 times ULN, respectively. While rosuvastatin and lovastatin had the two highest study period prevalence (51% and 50%, respectively) identified by ICD-9 codes and 1xULN of CK level, the prevalence dropped to 8% and 13%, respectively, when identified

by ICD-9 codes of 3 times and 5 times ULN of CK level. CK was checked for 40 patients in the control group, only one of these reported CK elevation more than 5 times ULN.

The AE prevalence for different age groups and genders is given in Table 5. Statins were more commonly prescribed for the elderly. Of 15,890 patients on statin, only 784 (5%) were in age group 31 to 40 and 8,906 (56%) were older than 60 years of age. Patients younger than 50 years of age had significantly lower AE prevalence than the older patients (3.7% vs. 6.5%; p-value < 0.001). Of 757 patients older than 50 years of age who were coded for AEs, only 295 (39%) were male. In age group 31 to 40, 11 of 18 patients (61%) reporting AE were male, but the difference did not reach statistical significance.

Discussion

The results suggest that patients on statin therapy report muscle and tendon related AEs much more frequently than the population not receiving statins. A very high percentage (97%) of patients reporting AEs did not have corresponding elevated CK values beyond three times the ULN. The high rate of AEs reported without elevated CK values suggest strong consideration for potential muscle damage even when not confirmed by elevated CK values. The current study also found that female patients had greater AE reporting without the corresponding elevated CK levels. This was emphasized in [21].

The FDA has recently issued a drug safety communication with new restrictions, contraindications, and dose limitations for simvastatin to reduce the risk of muscle injury [17]. The authors found that in the study population prior to the issuance of this warning, those on simvastatin had the lowest overall prevalence for the study period. The statins ranked in order of overall study period prevalence for muscle and tendon related AEs based on ICD9 codes were: simvastatin, atorvastatin, pravastatin, lovastatin, rosuvastatin, and fluvastatin. The FDA warning recommends limiting the use of the highest approved dose of simvastatin (80 mg) because of the increased risk of muscle damage [17]. However, the study period prevalence of coded AEs in this study at 80mg of simvastatin was not significantly higher than the overall study period prevalence (5.56% vs. 4.48%; p-value = 0.207). Similarly, the remaining statins did not have higher study period prevalence for their highest doses. Fluvastatin, lovastatin, and rosuvastatin at highest dose had only marginally higher study period prevalence than the overall prevalence. The

findings suggest that all statins, even at lower doses should be carefully monitored for muscle and tendon related AEs, and this risk should be balanced against statin benefits.

The study period AE prevalence based on ICD9 criteria was significantly higher among patients on rosuvastatin versus other statins. Pharmacokinetic differences in statins can affect potential drug interactions with statins and myotoxicity [22, 23]. Rosuvastatin is less subject to pharmacokinetic interactions with other concomitant drugs than any other statins [5]. This statin is also less lipophilic than any other statins [22, 24]. Although the pharmacokinetic differences are likely to have a lower risk of drug-drug interaction [22, 23], the finding in the current study suggests that this statin may induce higher rates of muscle and tendon related symptoms when used as monotherapy. The finding on rosuvastatin in the current study is consistent with the results from the previous studies [16, 25] and supports concerns that rosuvastatin may not be safer and better tolerated than the other statins in contrast to what has been reported [16, 25, 26]. The authors also found that another hydrophilic statin, pravastatin, had relatively higher prevalence when identified by CK elevations, but the difference did not reach statistical significance. As pointed out in the previous study [16], the finding in the current study has important implications regarding to statin therapy for patients who had muscle and tendon related AEs.

Moreover, fluvastatin was relatively rarely prescribed, but had an associated AE risk as high as rosuvastatin for all muscle categories [16]. The tendon related AE prevalence (18%) in the current study is comparable to 25% of statin-related tendon-associated pain [18]. The AE prevalence was significantly higher in female regardless of CK elevations (7.1% vs. 4.0%; p-value < .001). There was no gender difference for checking CK levels. However, the male population had greater prevalence in ICD9+CK3 (17/27 patients; 63%) and ICD9+CK5 (11/17 patients; 65%) cases. The greater AE reporting in female without CK elevations was discussed in [21].

Statin prescription and AE prevalence varied among different age groups and by gender. Relative risks for AE prevalence increased in the population with age > 50 years. While there was no gender difference of the AE prevalence in younger age groups (age <= 50 years), in older age groups (age > 50 years) male patients had significantly lower AE prevalence than female patients. The current study findings suggest that statin related AEs as ascertained by diagnosis codes were associated with patient age and gender.

To the best of our knowledge, this is the first comprehensive study of muscle and tendon related statin AEs using a large retrospective medical database. The use of electronic medical records allowed the identification and classification of large patient populations for different types of statins and AEs, which were further analyzed for AE study period prevalence and incidence rates during the 7-year study period. The actively managed patients were defined and identified in the current study. An extensive list of ICD-9 codes and the different levels of CK elevations were used to identify the corresponding AEs. The current study contributes to an important reference that provides exhaustive AE analyses based on the patient medical records obtained from Northwestern University affiliates.

The current study has the limitation that cases were determined by electronic medical records and lab data, but no attempt was made for a further manual chart review of the data. This creates a potential bias in assessing AE prevalence as this condition is often under reported. However, it is also possible that in a relative comparison this bias is canceled out. The current study was also limited because it did not control for medications not on the list that might result in myotoxicity. Further, being retrospective, not all patients with AEs had CK levels assessed. While this may underreport the ICD-9+CK prevalence, the relative risk versus controls was increased similarly to the case without CK elevations. This study also did not control for other behaviors and events resulting in an elevated CK value. Finally, while the study controlled for several common potentially interacting agents, it did not control for all interacting agents that could be prescribed with statins.

In summary, the results in the current study suggest that patients on statin therapy have a more than 30-fold increased AE prevalence. The AE prevalence was higher among patients on fluvastatin or rosuvastatin. However, the AE prevalence was not significantly higher at the highest dose of statins. Furthermore, among patients tested for CK, we found that the prevalence of AEs recorded without corresponding CK elevations were significantly higher than those with CK elevations. The relative risk of statin related AEs increased with patient age and were greater for female.

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Table 1. Characteristics of actively managed patients on different types of statins during the study period.

Drug name	Actively managed patients, no	Age, mean (SD)	Male, no (%)	CK checked, no (%)	CK checked male, no (%)
Atorvastatin	9514	63.8 (13.4)	5271 (55.4)	1223 (12.9)	638 (52.2)
Pravastatin	1574	64.5 (13.1)	735 (46.7)	252 (16.0)	119 (47.2)
Simvastatin	6921	63.8 (13.7)	3777 (54.6)	786 (11.4)	411 (52.3)
Fluvastatin	205	68.1 (12.1)	100 (48.8)	49 (23.9)	28 (57.1)
Lovastatin	888	65.6 (13.5)	488 (55.0)	140 (15.8)	66 (47.1)
Rosuvastatin	1891	61.1 (12.5)	1081 (57.2)	304 (16.1)	174 (57.2)
All	15890	63.7 (13.6)	8724 (54.9)	1704 (10.7)	905 (53.1)

Table 2. Prevalence and incidence rate of muscle and tendon related adverse events among patients on different types of statins.

All AEs (ICD9: 359.4, 359.8, 359.89, 359.9, 359.9, 710.4, 726.5, 726.61, 726.64, 726.71, 726.72, 726.79, 726.90, 728.85, 728.87, 728.88, 728.89, 728.9, 729.1, 729.8x, 791.3, and E942.2)					
Drug name	AE in case, no (%)	Age, mean (SD)	Male, no (%)	AE in control, no (%)	Incidence rate (95% CI)
Atorvastatin	455 (4.78)	65.4 (12.3)	191 (42.0)	18 (0.19)	2.28 (2.08 – 2.50)
Pravastatin	100 (6.35)	64.4 (12.1)	37 (37.0)	5 (0.32)	4.01 (3.26 – 4.88)
Simvastatin	335 (4.48)	66.7 (13.3)	130 (38.8)	10 (0.14)	2.66 (2.38 – 2.96)
Fluvastatin	17 (8.29)	62.5 (9.0)	8 (47.1)	0	5.09 (2.96 – 8.15)
Lovastatin	65 (7.32)	65.9 (14.5)	27 (41.5)	2 (0.23)	4.12 (3.18 – 5.25)
Rosuvastatin	139 (7.35)	62.6 (12.1)	60 (43.2)	4 (0.21)	3.63 (3.05 – 4.28)
All	858 (5.40)	65.5 (12.8)	349 (40.7)	27 (0.17)	2.31 (2.16 – 2.47)
Myalgia and Myositis (ICD9: 729.1)					
Drug name	AE in case, no (%)	Age, mean (SD)	Male, no (%)	AE in control, no (%)	Incidence rate (95% CI)
Atorvastatin	160 (1.68)	64.1 (11.4)	53 (33.1)	2 (0.02)	0.78 (0.66 – 0.91)
Pravastatin	49 (3.11)	62.1 (11.9)	18 (36.7)	2 (0.13)	1.92 (1.42 – 2.53)
Simvastatin	121 (1.75)	64.3 (12.2)	35 (28.9)	4 (0.06)	0.93 (0.77 – 1.11)
Fluvastatin	14 (6.83)	63.8 (8.3)	6 (42.9)	0	4.17 (2.28 – 7.00)
Lovastatin	22 (2.48)	59.4 (13.8)	5 (22.7)	0	1.32 (0.83 – 2.00)
Rosuvastatin	87 (4.60)	62.0 (12.7)	41 (47.1)	1 (0.05)	2.23 (1.79 – 2.75)
All	317 (1.99)	63.2 (11.8)	107 (33.8)	4 (0.02)	0.83 (0.74 – 0.92)
Myopathy (ICD9: 359.4, 359.8, 359.89, and 359.9)					
Drug name	AE in case, no (%)	Age, mean (SD)	Male, no (%)	AE in control, no (%)	Incidence rate (95% CI)
Atorvastatin	6 (0.06)	62.8 (9.1)	1 (16.7)	2 (0.02)	0.03 (0.01 – 0.06)
Pravastatin	4 (0.25)	64.8 (10.7)	1 (25.0)	0	0.15 (0.04 – 0.39)
Simvastatin	5 (0.07)	60.4 (5.4)	0	0	0.04 (0.01 – 0.09)
Fluvastatin	2 (0.98)	55.5 (16.3)	2 (100)	0	0.57 (0.07 – 2.07)
Lovastatin	1 (0.11)	76.0	0	0	0.06 (0.00 – 0.33)
Rosuvastatin	10 (0.53)	63.2 (14.7)	5 (50.0)	0	0.24 (0.12 – 0.45)
All	21 (0.13)	62.4 (10.5)	5 (23.8)	1 (0.01)	0.05 (0.03 – 0.08)
Rhabdomyolysis (728.88 and 728.89)					
Drug name	AE in case, no (%)	Age, mean (SD)	Male, no (%)	AE in control, no (%)	Incidence rate (95% CI)
Atorvastatin	4 (0.04)	70.8 (14.1)	4 (100)	0	0.02 (0.01 – 0.05)
Pravastatin	2 (0.13)	71.5 (7.8)	2 (100)	0	0.08 (0.01 – 0.27)
Simvastatin	13 (0.19)	71.1 (11.0)	6 (46.2)	0	0.10 (0.05 – 0.17)
Fluvastatin	0	NA	NA	0	0
Lovastatin	4 (0.45)	61.8 (12.8)	1 (25.0)	0	0.24 (0.06 – 0.61)
Rosuvastatin	5 (0.26)	64.8 (11.3)	3 (60.0)	0	0.12 (0.04 – 0.28)
All	21 (0.13)	71.7 (10.5)	10 (47.6)	1 (0.01)	0.05 (0.03 – 0.08)
Joints and tendon (ICD9: 726.5, 726.61, 726.64, 726.71, 726.72, 726.79, and 726.90)					
Drug name	AE in case, no (%)	Age, mean (SD)	Male, no (%)	AE in control, no (%)	Incidence rate (95% CI)
Atorvastatin	91 (0.96)	64.6 (11.8)	34 (37.4)	7 (0.07)	0.44 (0.36 – 0.54)
Pravastatin	18 (1.14)	63.7 (10.5)	6 (33.3)	0	0.69 (0.41 – 1.09)
Simvastatin	54 (0.78)	62.6 (13.2)	22 (40.7)	3 (0.04)	0.41 (0.31 – 0.54)
Fluvastatin	1 (0.49)	59.0	0	0	0.29 (0.01 – 1.59)
Lovastatin	13 (1.46)	71.2 (11.1)	2 (15.4)	0	0.78 (0.41 – 1.33)
Rosuvastatin	21 (1.11)	62.9 (10.8)	7 (33.3)	0	0.51 (0.32 – 0.79)
All	154 (0.97)	63.8 (12.3)	57 (37.0)	6 (0.04)	0.40 (0.34 – 0.47)

Injury (ICD9: 728.85)					
Drug name	AE in case, no (%)	Age, mean (SD)	Male, no (%)	AE in control, no (%)	Incidence rate (95% CI)
Atorvastatin	0	NA	0	0	0
Pravastatin	0	NA	0	0	0
Simvastatin	2 (0.03)	73.5 (9.2)	1 (50.0)	0	0.02 (0.00 – 0.05)
Fluvastatin	0	NA	0	0	0
Lovastatin	0	NA	0	0	0
Rosuvastatin	0	NA	0	0	0
All	2 (0.01)	73.5 (9.2)	1 (50.0)	0	0.01 (0.00 – 0.02)
Weakness (ICD9: 728.87 and 728.9)					
Drug name	AE in case, no (%)	Age, mean (SD)	Male, no (%)	AE in control, no (%)	Incidence rate (95% CI)
Atorvastatin	52 (0.055)	69.4 (13.3)	28 (53.8)	1 (0.01)	0.25 (0.19 – 0.33)
Pravastatin	4 (0.25)	82.0 (10.9)	0	0	0.15 (0.04 – 0.39)
Simvastatin	46 (0.66)	70.0 (12.5)	21 (45.7)	0	0.35 (0.26 – 0.47)
Fluvastatin	0	NA	0	0	0
Lovastatin	8 (0.90)	73.5 (12.9)	5 (62.5)	0	0.47 (0.20 – 0.94)
Rosuvastatin	8 (0.42)	65.8 (15.1)	2 (25.0)	0	0.19 (0.08 – 0.38)
All	103 (0.65)	69.9 (13.3)	47 (45.6)	4 (0.03)	0.26 (0.22 – 0.32)
Polymyositis, Musculoskeletal Symptoms, and Myoglobinuria (ICD9: 710.4, 791.3, and 729.8x)					
Drug name	AE in case, no (%)	Age, mean (SD)	Male, no (%)	AE in control, no (%)	Incidence rate (95% CI)
Atorvastatin	189 (1.99)	66.7 (12.6)	84 (44.4)	5 (0.05)	0.92 (0.80 – 1.07)
Pravastatin	32 (2.03)	67.2 (11.8)	13 (40.6)	1 (0.06)	1.24 (0.85 – 1.75)
Simvastatin	126 (1.82)	68.6 (13.7)	51 (40.5)	5 (0.07)	0.97 (0.81 – 1.16)
Fluvastatin	0	NA	0	0	0
Lovastatin	28 (3.15)	68.6 (14.6)	16 (57.1)	0	1.70 (1.13 – 2.46)
Rosuvastatin	21 (1.11)	65.0 (10.2)	6 (28.6)	1 (0.05)	0.51 (0.32 – 0.78)
All	333 (2.10)	67.4 (13.1)	142 (42.6)	8 (0.05)	0.87 (0.78 – 0.97)

Table 3. Number of patients taking higher dose of different statins

Drug name (dose)	Actively managed patients with dose, no	Actively managed patients taking higher dose, no	ICD9 case taking higher dose, no	Highest Dose AE prevalence, % (95% CI)	Overall Prevalence, %	P value
Atorvastatin (80mg)	2737	129	5	3.88 (1.44 – 9.27)	4.78	0.743
Pravastatin (80mg)	870	108	6	5.56 (2.28 – 12.2)	6.35	0.689
Simvastatin (80mg)	2967	324	18	5.56 (3.42 – 8.79)	4.48	0.207
Fluvastatin (80mg)	165	62	9	14.5 (7.25 – 26.3)	8.29	0.069
Lovastatin (40mg)	202	88	10	11.4 (5.88 – 20.3)	7.32	0.109
Rosuvastatin (40mg)	710	106	6	5.66 (2.32 – 12.4)	7.35	0.074

Table 4. CK value distribution in AE population.

Drug name	CK checked in ICD9 case, no	AEs in ICD9+CK1 case, no (%)	AEs in ICD9+CK3 case, no (%)	AEs in ICD9+CK5 case, no (%)
Atorvastatin	140	52 (37%)	14 (10%)	6 (4%)
Pravastatin	35	16 (45%)	6 (17%)	4 (11%)
Simvastatin	89	42 (47%)	10 (11%)	8 (9%)
Fluvastatin	7	1 (14%)	1 (14%)	0
Lovastatin	24	12 (50%)	3 (13%)	2 (8%)
Rosuvastatin	59	30 (51%)	5 (8%)	1 (2%)
All	259	109 (42%)	27 (10%)	17 (7%)

Table 5. Prevalence of muscle and tendon related adverse events among patients on statin in different age groups and gender.

Age range	Patients on statin, no	AEs, no (%)	AEs in Male, no (% of AEs)
31 to 40	784	18 (2.30)	11 (61.1)
41 to 50	1972	83 (4.21)	44 (53.0)
51 to 60	2797	201 (5.29)	78 (38.8)
61 to 70	4460	260 (5.83)	97 (37.3)
71 to 80	2830	174 (6.15)	69 (39.7)
Greater than 80	1616	122 (5.93)	50 (41.0)